REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The rejection of claims 6-8 under 35 U.S.C. § 112 (first paragraph) for indefiniteness is respectfully traversed in view of the above amendments.

The rejection of claims 6-7 and 14-15 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,015,787 to Potter et al. ("Potter") is respectfully traversed in view of the above amendments and should be withdrawn.

The rejection of claims 6-8 and 14-16 under 35 U.S.C §103 as obvious over U.S. Patent No. 5,478,727 to Roizman et al. ("Roizman"), U.S. Patent No. 5,607,831 to Henkart et al. ("Henkart"), Kido et al., Advances in Enzyme Regulation, 36:325-347 (1996) ("Kido") and de Jong et al., Antiviral Research, 39:141-162 (1998) ("de Jong") is respectfully traversed.

Roizman relates to the identification and purification of a herpes protease. Roizman solely discloses **viral** proteases; Roizman does not, however, relate to decreasing levels of functional **cellular** protease in cells. The outstanding office action indicates that Roizman suggests target proteases which are vital to the viral life cycle, however, Roizman exclusively relates to viral proteases. Nowhere does Roizman disclose or suggest cellular proteases. Further, Roizman does not teach or suggest calpain inhibitors.

Henkart relates to calpain inhibitors and their use in preventing the progression of cell death, especially in individuals with HIV. Again, Henkart, like Roizman, do not relate to decreasing levels of functional **cellular** protease in cells. Further, Henkart does not relate to HCMV, but exclusively discloses HIV.

Kido relates to the cellular proteases involved in the pathogenicity of enveloped animal viruses, HIV, influenza virus A and Sendai virus. Kido does not relate to calpain inhibitors, nor does Kido relate to human cytomegalovirus.

de Jong relates to human cytomegalovirus and its persistence in latent form. de Jong further discloses CMV disease in HIV-infected persons being caused by reactivation of latent virus. de Jong, does not relate to calpain inhibitors or to methods of decreasing viral replication of a human cytomegalovirus.

Firstly, Roizman, Henkart, Kido and de Jong are not properly combinable. One skilled in the art of Roizman, which relates to identification of a herpes protease, would have no reason to look at Henkart, Kido or de Jong for answers relating to identification and purification of a herpes protease. Likewise, one skilled in the various arts of Henkart (calpain inhibitor in treatment for HIV), Kido (activation of animal enveloped viruses) and de Jong (latent HCMV virus associated with HIV) would not have been motivated to look at the other art for answers relating to their art. It appears to be the reasoning of the U.S. Patent and Trademark Office ("PTO") that one skilled in the art would have been motivated to combine the references because de Jong teaches individuals with HIV infection also have HCMV infection and that Roizman suggests treating viral infections using target proteases which are vital to the viral life cycle. However, the PTO has provided no basis as to why one skilled in the art would have looked to any of the other references for a calpain inhibitor to treat HCMV infection. The references only disclose calpain inhibitors for treating HIV infection. NONE of the references (and therefore, likewise, the combination of the references in total) teach or suggest use of a calpain inhibitor to treat HCMV. There is no motivation in any of the references, or in the state of the

art, to suggest to one skilled in the art to use the calpain inhibitors of Henkart to treat anything other than HIV. Even if, assuming *arguendo*, that (1) a motivation to combine the references is provided by Roizman and de Jong, which applicants submit it is not and (2) the teaching of Roizman is as stated in the outstanding office action, which applicants submit it is not, the cited combination would only teach, at most, a method of treating HIV infection by decreasing levels of functional cellular protease in the cells by exposing the cells to a calpain inhibitor. The fact that de Jong teaches CMV disease in HIV-infected persons being caused by reactivation of latent virus does not provide motivation to treat CMV disease in a manner similar to treatment of HIV. Further, a statement such as set out in the outstanding office action on page 8 that

> "the prior art as a whole teaches methods of inhibiting herpes viral replication and treating herpes viral infections by inhibiting proteases vital to the herpes viral lifecycle and that these methods are generally applicable to other members of the herpes virus family, including cytomegalovirus and that cellular proteases were known to be proteases that were vital to the lifecycle of enveloped viruses"

appears to employ an "obvious to try" standard.

An "obvious to try" standard is improper and the combination further appears to be based on impermissible hindsight (See MPEP (X)(A)-(B)). Prior to the present invention, there was no suggestion, either in the references, or in the state of the art, to treat viral replication of a HCMV with a calpain inhibitor. As discussed above, the cited references do not provide such motivation. One skilled in the art, having reviewed the cited references, would not have been motivated to use calpain inhibitors generally, nor the

specifically identified calpain inhibitors, because there is no suggestion in de Jong, Kido or Roizman to modify Henkart to treat HCMV. As discussed above, Henkart relates to the treatment of HIV. Roizman relates to treatment of herpes viruses, via viral proteases. Therefore, any suggestion Roizman provides would be for modifying Henkart to treat viral replication by decreasing viral proteases, not cellular proteases as claimed in the present application. This deficiency is not overcome by de Jong, which merely recognizes the association of HIV with latent HCMV. Neither is this deficiency overcome by Kido, which discusses cellular proteases. Firstly, Kido does not suggest that decreasing levels of cellular proteases by any means, let alone calpain inhibitors generally or the specified calpain inhibitors, may be useful in the treatment of the viruses disclosed in Kido. Secondly, Kido, which does not disclose or suggest HCMV at all, does not suggest that decreasing levels of cellular proteases will be useful in decreasing viral replication of HCMV.

Contrary to the assertion in the outstanding office action, applicants are not arguing the references individually as if the rejection was under 35 U.S.C. § 102. Applicants instead are pointing out that none of the references teach or suggest using the specified calpain inhibitors to treat HCMV, therefore, the combination of references likewise does not teach or suggest the present invention.

For all of the above reasons, the rejections of claims 6-8 and 14-16 under 35 U.S.C §103 as obvious over the cited references is improper and must be withdrawn.

The rejection of claims 8 and 16 under 35 U.S.C. § 103 as obvious over Henkart and de Jong in view of U.S. Patent No. 6,015,787 to Potter ("Potter") is respectfully traversed.

Potter relates to a fusion protein which includes a first portion that is capable of delivering the fusion protein

into a cell and a second portion which includes a calpastatin peptide.

As discussed above in detail, Henkart and de Jong are not properly combinable. Further, Henkart and de Jong do not teach or suggest a method of decreasing viral replication of a human cytomegalovirus where the calpain inhibitor increases the levels of $p21^{cip}$ nor do they teach or suggest a method of decreasing viral replication of a human cytomegalovirus in cells, the method comprising decreasing levels of functional cellular protease. Potter does not overcome these deficiencies. Further, neither Henkart or de Jong suggest modifying Potter to utilize the particular calpain inhibitors, because Potter teaches that a fusion protein must be used to have a portion which will enter the cell. There is no suggestion in any of the references that Potter could be modified to use a calpain inhibitor alone (i.e. not a fusion protein). As the outstanding office action points out, Henkart does teach a calpain inhibitor, however, applicants point out, and as stated above, there is no suggestion in any of the references that Potter could be modified to use a calpain inhibitor alone. Potter teaches the use of a fusion protein which includes calpain. However, Potter must be considered for all of its teaching, including any teaching away. Potter exclusively teaches that in order to enter a cell, a fusion protein which includes a portion capable of delivering the fusion protein into a cell must be used. Accordingly, one skilled in the art of Potter, Henkert and/or de Jong, after reviewing the disclosure of Potter, would not have been motivated to consider a method of decreasing viral replication of a human cytomegalovirus in cells, the method including decreasing levels of functional cellular protease in the cells by exposing the cells to E64D or Z-Leu-Leu-H, because Potter teaches fusion proteins must be used.

In view of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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